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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/335,218	06/17/99	WRIGHT D	P-4423

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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/335,218	WRIGHT ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *04 August 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *25-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 55-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 18 July 2000 in Paper No. 6 in which claims 13 and 18 were amended and claims 55-62 were added. All of the amendments have been thoroughly reviewed and entered. All of the arguments have been thoroughly reviewed and are discussed below. The previous rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 102(e) and 35 U.S.C. 103(a) are withdrawn in view of the amendments. New grounds for rejection are discussed.

2. Currently claims 1-24 and 55-62 are under prosecution.

Election/Restrictions

3. Applicant's election with traverse of Invention I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the inventions of Group I and Group II are not unrelated because they are connected in operation by employment of detector primers which are similar in structure and they are connected in operation and effect because both methods rely on the determination of the efficiency of extension of the detector primer. This is not found persuasive because as stated in the restriction requirement the different inventions have different modes of operation, different functions and different method steps.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-5, 14-18 & 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding Claim 1, Schram et al. disclose the method for detecting a target region having a single nucleotide difference (Column 4, lines 56-67 and Column 5, lines 1-5) in a target comprising hybridizing a detector primer i.e. SEQ ID NO: 1 and a second primer i.e. SEQ ID NO: 4 (Example 4, Column 10, lines 24-27 and Column 5, Table 1) to the target such that extension of the second primer by polymerase displaces the detector primer from the target sequence (Column 3, lines 53-58) wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide difference which is the 3' terminal nucleotides of the detector primer (Column 5, lines 18-27), extending the detector primer and the second primer with polymerase to produce a displaced detector primer extension product (Column 3, lines 56-59), determining the efficiency of detector primer extension (Column 7, lines 37-52), and detecting the presence or absence of the target region having the single nucleotide difference based on the efficiency of detector primer extension (Example 1, Column 8, Table 2 and Example 4, Column 10, lines 49-52). The method of Schram et al. includes an amplification step however, the open claim language "comprising" recited in the instant claim encompasses the addition of an amplification step.

Regarding Claim 2, Schram et al. disclose the method of Claim 1 wherein the single nucleotide difference is identified using the detector primer (Column 7, line 37-41).

Regarding Claim 3, Schram et al. disclose the method of Claim 2 wherein the single nucleotide difference is identified using multiple detector primers i.e. SEQ ID NO: 1 & 3 (Example 4, Column 10, lines 24-26) each comprising a different diagnostic nucleotide (Column 5, Table 1).

Regarding Claim 4, Schram et al. disclose the method of Claim 3 wherein two detector primers are used to identify which of two possible target sequences are present (Example 4, Column 10, lines 25-26 and Column 5, Table 1).

Regarding Claim 5, Schram et al. disclose the method of Claim 3 wherein four detector primers are used i.e. SEQ ID NO: 1, 3, 11 & 12 (Example 4, Column 10, lines 25 and 34-36) wherein SEQ ID NO: 11 & 12 are detector probes extended in a primer extended in a primer extension assay (Column 10, lines 31-36).

Regarding Claim 14, Schram et al. teach the method of Claim 13 wherein the amplification reaction is selected from the group PCR, SDA and 3SR (Column 6, lines 49-53).

Regarding Claims 15-17, Schram et al. teach the method of Claim 1 wherein the detector primer is about 12-50, 12-24, and 12-19 nucleotides long (Column 5, Table 1).

Regarding Claim 18, Schram et al. teach the method of Claim 1 wherein the presence or absence of the single nucleotide difference is detected by means of a label associated with the detector primer (Column 7, lines 39-41).

Regarding Claim 24, Schram et al. teach the method of Claim 1 wherein the efficiency of detector primer extension is determined quantitatively (Example 1, Table 2 and Example 4, Column 10, lines 49-53).

Response to Arguments

6. Applicant argues that Schram et al. do not teach differences in primer extension efficiency as the basis for detecting sequence differences because their primers results in equal amplification efficiency of the target. This argument is not found persuasive because, as cited

above, Schram et al. clearly teaches a difference in primer extension efficiency resulting from a single nucleotide difference between targets (Column 10, lines 49-67).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Schram et al. in view of Walker et al.

8. Claims 6-13 are rejected under 35 U.S.C. 103(a) as being obvious over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to Claim 1 above in view of Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 6, Schram et al. teach the method of Claim 3 wherein each of the detector primers has a 5' restriction enzyme recognition sequence (Column 3, lines 34-36). Schram et al. do not teach each of the detector primers has a different 5' sequence. However, detector primers having a different 5' sequence i.e. methylated or unmethylated was known in the art as taught by Walker et al. Column 10, lines 2-22 and 32-66). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Schram et al. with the teaching of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to construct primers having a different 5' restriction enzyme recognition sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 7, Schram et al. teach the method of Claim 1 wherein the detector primer has a 5' non-diagnostic restriction enzyme recognition sequence but they do not teach the non-diagnostic sequence forms mismatch with the target sequence. However, primers having 5' non-diagnostic mismatch were known in the art at taught by Walker et al. (Column 8, lines 33-35 and Fig. 1, S1 and S2) who teach the 5' non-diagnostic mismatch is an enzyme recognition site. It would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Schram et al. with the teaching of Walker et al. to obtain the claimed invention because one skill in the art would have been motivated with a reasonable expectation of success to modify the restriction sequence of Schram et al. with the mismatched restriction sequence of Walker et al. for the expected benefit of producing quantities of amplified fragments having defined ends (Walker et al. , Column 4, lines 53-59).

Regarding Claims 8-10 Schram et al. teach the method of Claims 1 & 7 wherein the non-diagnostic nucleotide i.e. 5' restriction enzyme recognition sequence, GTTG is within 15 nucleotides i.e. adjacent to the diagnostic nucleotide (Column 5, Table 1). Schram et al. do not teach the recognition sequence is a mismatch and they do not teach the mismatch is 1-5 nucleotides from the diagnostic nucleotide. However, detector primers having a non-diagnostic mismatch within fifteen nucleotides of the diagnostic nucleotide were known in the art as taught by Walker et al. Specifically, Walker et al. teach the non-diagnostic mismatch i.e. 5' restriction enzyme recognition sequence is within 15 nucleotides of the diagnostic nucleotide wherein the primers are 20-100 nucleotides (Column 8, lines 27-28) and the enzyme recognition sequences are 5-19 nucleotides (Column 10, lines 30-66). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Schram et al. with the Walker et al. teaching to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the Walker et al. primers having the diagnostic nucleotide

proximal to the enzyme-recognition mismatches to the method of Schram et al. for obvious benefit increased binding efficiency and reduced cost of primer synthesis.

Regarding Claim 11, Schram et al. teach the detector primers are 15-36 nucleotides long (Column 5, Table 1) and Walker et al. teach the detector primers are 15-36 nucleotides long (Column 8, line 30).

Regarding Claim 12, Schram et al. teach the detector primers are 18-24 nucleotides long (Column 5, Table 1) and Walker et al. teach the detector primers are 18-24 nucleotides long (Column 8, line 30).

Regarding Claim 13, Schram et al. teach the method of Claim 1 wherein the second primer is a bumper primer (Column 3, lines 53-56). Schram et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art as amplification primers wherein the first step in amplification is primer extension. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made that amplification primers were also extension primers.

Response to Arguments

9. Applicant argues that Schram et al. do not teach differences in primer extension efficiency as the basis for detecting sequence differences because their primers results in equal amplification efficiency of the target. Applicant further argues that Walker et al. do not overcome the deficiency of Schram et al. This argument is not found persuasive recited above.

Schram et al. in view of Walker et al.

10. Claims 19-21 are rejected under 35 U.S.C. 103(a) as being obvious over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to Claim 18 above in view of Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 19, Schram et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al.

teach a similar method for detecting a target sequence using detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Regarding Claim 20, Schram et al. teach the method of Claim 18, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a target sequence wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57).

Regarding Claim 21, Schram et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al. teach a similar method for detecting a target sequence using detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Response to Arguments

11. Applicant argues that Schram et al. do not teach differences in primer extension efficiency as the basis for detecting sequence differences because their primers results in equal amplification efficiency of the target. Applicant further argues that Walker et al. do not overcome the deficiency of Schram et al. This argument is not found persuasive recited above.

Schram et al. in view of Thomas et al.

12. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Schram et al teach the method of Claim 1 wherein a single nucleotide difference is detected in a target sequence. Schram et al do not teach the method wherein a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis (HH) was known to have a single nucleotide difference i.e. mutation in exon 4 as taught by Thomas et al. (Column 16, lines 25-33). Thomas et al. teach a single nucleotide difference in exon 4 i.e. 24d1 wherein

the mutation is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific amplification and detection of the 24d1 mutation (Column 17, lines 1-4 and Fig 6A). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Schram et al. with the teaching of Thomas et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to apply the target-specific amplification method of Schram et al. to the primer and target sequences taught by Thomas et al. for the expected benefit of efficient diagnosis of disease-causing mutations.

Response to Arguments

13. Applicant argues that Schram et al. do not teach differences in primer extension efficiency as the basis for detecting sequence differences because their primers results in equal amplification efficiency of the target. Applicant further argues that Thomas et al. do not overcome the deficiency of Schram et al. This argument is not found persuasive recited above.

Vary et al. in view of Schram et al. and Walker et al.

14. Claims 1-22 & 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Schram et al. (U.S. Patent No. 5681,705, filed 28 August 1995) and Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 1, Vary et al. disclose the method for detecting a single nucleotide difference in a target (Column 1, lines 47-50 and Column 2, lines 35-38 and Example 3) comprising hybridizing a detector primer wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide difference which is the 3' terminal nucleotides of the detector primer (Column 1, lines 57-65 and Example 3, Column 12, lines 21-22), extending the detector primer with polymerase to produce a detector primer extension product (Column 1, lines 65-68 and Example 3, Column 12, lines 26-50), determining the efficiency of detector primer extension (Column 12, lines 52-68 and Table 5), and detecting the presence or absence

of the single nucleotide difference based on the efficiency of detector primer extension (Example 3, Column 12, lines 57-60 and Table5). Vary et al. teach the method for detecting a single nucleotide difference but they do not teach the method wherein the primer extension product is displaced by extension of a second primer. However, displacement of primer extension product i.e. strand displacement was known in the art as taught by Schram et al. who teach a similar method for detecting a single nucleotide difference wherein the primer extension is dissociated from the template by extension of an upstream primer (Column 3, lines 61-64). It would have been *prima facie* obvious to one of ordinary skill in the art to modify the Vary et al. method with the teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the strand displacement teaching of Schram et al. to the method of Vary et al. for the obvious benefit of producing a quantity of extension product.

Regarding Claim 2, Vary et al. disclose the method of Claim 1 wherein the single nucleotide difference is identified by labeled primer extension product (Example 3, Column 12, lines 55-60 and Table 5). Vary et al do not teach identification using the detector primer. However, primer labeling was routinely practiced in the art at the time the claimed invention was made as an alternative to incorporation of label into the primer extension product. It would have been *prima facie* obvious to one of skill in the art to modify the method of Vary et al. and label the primer because the skilled practitioner would have been motivated with a reasonable expectation of success to used labeled primers based on the commercial availability of labeled primers and desired results.

Regarding Claim 3, Vary et al. disclose the method of Claim 2 wherein the single nucleotide difference is identified using multiple detector primers each comprising a different diagnostic nucleotide (Example 3, Column 12, lines 21-25).

Regarding Claim 4, Vary et al. disclose the method of Claim 3 wherein two detector primers are used to identify which of two possible target sequences are present (Example 4, Column 13).

Regarding Claim 5, et al. Vary et al. do not disclose the method of Claim 3 wherein four detector primers are used. However, multiple detector primers were known in the art as taught by Schram et al. who teach similar method for detecting a single nucleotide difference wherein four detector primers are used i.e. SEQ ID NO: 1, 3, 11 & 12 (Example 4, Column 10, lines 25 and 34-36). It would have been *prime facie* obvious to one of skill in the art to modify the method of Vary et al. with the teaching of Schram et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the multiple detector primer teaching of Schram et al. to the method of Vary et al. for the expected benefit of specifically identifying multiple species in a complex sample.

Regarding Claim 6, Vary et al. teach the method of Claim 3 wherein each of the detector primers have a specific 5' recognition sequence (Column 7, lines 26-30 and Fig. 3) and they teach numerous 5' tails. Vary et al. do not teach each of the detector primers has a different 5' sequence. However, it would have been *prima facie* obvious to one of ordinary skill in the art modify the primers of Vary et al. with the teaching of Vary et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the teaching of Vary et al. to construct primers wherein each has a different 5' sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 7, Vary et al. teach the method of Claim 1 wherein the detector primer has a 5' non-diagnostic recognition sequence which forma non-diagnostic mismatch with the target sequence (Column 7, lines 26-30 and Fig. 3)

Regarding Claims 8-10 Vary et al. teach the method of Claim 1 wherein the non-diagnostic nucleotide is within 15 nucleotides i.e. adjacent to the diagnostic nucleotide. Specifically, Vary et al. teach the detector primes are 10 nucleotides in length (Column 2, lines 52-23) having a 5'non-diagnostic mismatch and a 3' diagnostic nucleotide (Column 7, lines 24-28). Therefore, it would have been prima facie obvious to one of ordinary skill in the art that the non-diagnostic nucleotides and the diagnostic nucleotide are within 15 nucleotides, positioned 1-5 nucleotides apart, and/or adjacent and the skilled practitioner would have been motivated with a reasonable expectation of success to construct primers having defined 5' to 3' proximity based on the size of the target region and for known benefit of synthesizing smaller primers chemically as taught by Vary et al. (Column 2, lines 52-54).

Regarding Claims 11 & 12, Vary et al. teach the detector primers are 15-36 nucleotides long and 18-24 nucleotides long (Column 2, lines 52-53).

Regarding Claim 13, Vary et al. teach the method of Claim 1 wherein the second primer is an extension primer (Example 3, Column 12, lines 20-22). Vary et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art as amplification primers wherein the first step in amplification is primer extension. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made that amplification primers were also extension primers.

Regarding Claim 14, Vary et al. teach the method of Claim 13 wherein the extension reaction is performed in the presence of AMV Reverse Transcriptase (Example 3). However, Schram et al. teach a similar method for detecting a single nucleotide difference wherein the detection method includes an amplification reaction i.e. SDA (Column 4, line 67 through Column 5, lines 1-5). It would have been *prime facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the SDA teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply SDA to the method of

Vary et al. for the expected benefit of species-specific target region detection as taught by Schram et al. (Column 4, lines 48-50)

Regarding Claims 15-17, Vary et al. teach the method of Claim 1 wherein the detector primer is about 12-50, 12-24, and 12-19 nucleotides long (Column 2, lines 52-53).

Regarding Claim 18, Vary et al. teach the method of Claim 1 wherein the presence or absence of the single nucleotide difference is detected by means of a label associated with the detector primer (Example 2, Column 11, lines 60-62) wherein the label is associated with the detector primer by virtue of the primer extension product.

Regarding Claim 19, Vary et al. teach the method of Claim 18 wherein the label becomes detectable upon extension of the primer due to the incorporation of labeled nucleotides (Column 3, lines 54-59, Fig 1E and Fig 4F)

Regarding Claim 20, Vary et al. teach the method of Claim 18, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a single nucleotide difference in a target sequence by detection of the detector primer extension wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57).

Regarding Claim 21, Vary et al. teach the method of Claim 18, but they do not teach the label produces a change in signal upon extension of the primer. However, Walker et al. teach a the method for detection of the detector primer extension wherein a label produces a change in signal upon extension of the detector primer i.e. fluorescence polarization (Column 12, lines 51-55).

Regarding Claim 24, Vary et al. teach the method of Claim 1 wherein the efficiency of the detector primer extension is determined quantitatively (Example 3, Table 5). Specifically, Vary et al. teach the efficiency of detector primer extension is determined quantitatively by measuring the incorporation of labeled nucleotide into the extension product (Example 3, Table 5) and wherein the efficiency incorporation was dependent upon complementation between the

3' nucleotide of the primer and the template (Example 4, Column 13, lines 56-68 and Column 14, lines 1-4).

Response to Arguments

15. Applicant argues that Vary et al. in combination with Schram et al. and Walker et al. do not teach isothermal extension and displacement to obtain optimal discrimination of sequence variation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., isothermal extension and displacement to obtain optimal discrimination of sequence variation are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant further argues that Schram et al. Schram et al. do not teach differences in primer extension efficiency as the basis for detecting sequence differences because their primers results in equal amplification efficiency of the target. This argument is not found persuasive recited above.

Vary et al. and Schram et al. in view of Thomas et al.

13. Claims 22 & 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) and Schram et al. (U.S. Patent No. 5,681,705, filed 28 August 1995) as applied to claim 1 above, and further in view of Thomas et al. (U.S. Patent No. 6,025,130, filed 23 May 1996). Vary et al. and Schram et al. teach the method of Claim 1 wherein a single nucleotide difference is detected in a target sequence. Vary et al. and Schram et al do not teach the method wherein a single nucleotide difference in the HFE gene is detected. However, the HFE i.e. Hereditary Hemochromatosis gene (HH) was known to have a single nucleotide difference in exon 4 as taught by Thomas et al. (Column 11, lines 56-59 and Column 16, lines 59-65). Thomas et al. teach a single nucleotide difference i.e. mutation in exon 4 of the HH gene i.e. 24d1 (Column 16, lines 25-33) wherein the difference is responsible for the majority of hereditary hemochromatosis (Column 11, lines 63-64) and they teach primers for target-specific detection of the 24d1 difference (Column 17, lines 1-4 Fig 6A).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the method of Vary et al. and Schram et al. with the teaching of Thomas et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to apply the target-specific detection method of Vary et al. and Schram et al. to the primer and target sequences taught by Thomas et al. for the expected benefit of efficient gene-based diagnosis of disease-causing mutation.

Response to Arguments

14. Applicant argues that the combination of Vary et al., Schram et al. and Thomas et al. do not teach the claimed invention and therefore a case of prima facie obviousness is not established. This argument is not found persuasive for the reasons stated above.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-8, 11, 12, 15-18 & 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 7, 10 & 13 of U.S. Patent No. 5,681,705 filed 28 August 1995. Although the claims are not identical, they are not patentably distinct because both sets of claims are drawn to a method for detecting a single nucleotide difference in a target sequence using detector primers having 3' specificity for the target regions wherein the nucleotide difference is detected by extension of the detector primers. The only difference between the claim sets is that the patent claims recite an

amplification step in the method wherein amplification results in loss of the originally present mismatch (Column 6, lines 8-15). It would have been *prime facie* obvious to one of ordinary skill in the art to modify the patent method and to omit the amplification step wherein the function is not desired or required based on the obvious benefit of reducing time, labor and material costs. The courts have stated that it would be obvious to omit an element when a function attributed to said element is not desired or required (see Ex parte Wu, 10 USPQ 2031).

16. Claims 1-8, 11-18 & 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 7, 10 & 13 of U.S. Patent No. 5,681,705, filed 28 August 1995. Although the claims are not identical, they are not patentably distinct because both sets of claims are drawn to a method for detecting a single nucleotide difference in a target sequence using detector primers having 3' specificity for the target regions. The only difference is the patent claims recite amplification primers consisting of SEQ ID NO: 1, 2, 3 and the application claims recite detector primers. However, the patent defines the amplification primers contain a 3' single nucleotide which discriminates between perfect match and mismatch primer-target binding (Column 5, lines 17-34). Similarly, the application defines the detector primers contain a 3' nucleotide which discriminates between perfect match and mismatch primer-target binding (page 4, lines 2-7). Therefore, it would have been *prima facie* obvious to one of skill in the art to apply the patent primer teaching to the patent method to obtain the claimed invention for the expected benefit of universal detection of single nucleotide differences.

Response to Arguments

17. Applicant argues that Schram et al. do not teach detecting sequence variation based on primer extension efficiency. This argument is not found persuasive because, as cited above, Schram et al. clearly teaches a difference in primer extension efficiency resulting from a single nucleotide difference between targets (Column 10, lines 49-67).

New Claims

18. Claims 55-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Schram et al. (U.S. Patent No. 5681,705, filed 28 August 1995) and Walker et al. (U.S. Patent No. 5,270,184, filed 19 November 1991).

Regarding Claim 55, Vary et al. teach the method for detecting a single nucleotide difference in a target sequence (Column 1, lines 47-50 and Column 2, lines 35-38 and Example 3) comprising hybridizing to the target sequence a detector primer comprising a diagnostic nucleotide for the single nucleotide difference (Column 1, lines 57-65 and Example 3, Column 12, lines 21-22), extending the detector primer with polymerase to produce a detector primer extension product (Column 1, lines 65-68 and Example 3, Column 12, lines 26-50), and detecting the presence or absence of the single nucleotide difference based on the efficiency of detector primer extension (Example 3, Column 12, lines 57-60 and Table5). Vary et al. teach the method for detecting a single nucleotide difference but they do not teach the method wherein the primer extension product is displaced by extension of a second primer. However, displacement of primer extension product i.e. strand displacement was known in the art as taught by Schram et al. who teach a similar method for detecting a single nucleotide difference wherein the primer extension is dissociated from the template by extension of an upstream primer (Column 3, lines 61-64). It would have been *prima facie* obvious to one of ordinary skill in the art to modify the Vary et al. method with the teaching of Schram et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the strand displacement teaching of Schram et al. to the method of Vary et al. for the expected benefit of producing extension products which can be amplified taught by Schram et al. (Column 3, liens 53-54).

Regarding Claim 56, Vary et al. do not teach the single nucleotide polymorphism is identified using the detector primer. However, Schram et al. teach a similar method for detecting a single nucleotide difference wherein the difference is identified using the detector primer (Column 7, line 37-41).

Regarding Claim 57, Vary et al. teach the method wherein the single nucleotide difference is identified using multiple detector primer each comprising a different diagnostic nucleotide (Column 12, lines 21-25) and Schram et al. teach the method wherein the single nucleotide difference is identified using multiple detector primers i.e. SEQ ID NO: 1 & 3 (Example 4, Column 10, lines 24-26) each comprising a different diagnostic nucleotide (Column 5, Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Schram et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Vary et al. with the detector primer and multiple detector primers of Schram et al. for the obvious benefit of specifically detecting diagnostic component.

Regarding Claim 58, Vary et al. teach the method of Claim 3 wherein each of the detector primers have a specific 5' recognition sequence (Column 7, lines 26-30 and Fig. 3) and they teach numerous 5' tails. Vary et al. do not teach each of the detector primers has a different 5' sequence. However, detector primers having a different 5' sequence i.e. methylated or unmethylated was known in the art as taught by Walker et al. (Column 10, lines 2-22 and 32-66). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teaching of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to construct primers having a

different 5' restriction enzyme recognition sequence for the expected benefit of specific and rapid isolation and identification of primer extension products.

Regarding Claim 59, Schram et al. teach the method of Claim 1 wherein the second primer is a bumper primer (Column 3, lines 53-56). Schram et al. do not teach the second primer is an amplification primer. However, extension primers were routinely used in the art as amplification primers wherein the first step in amplification is primer extension. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the time the claimed invention was made to modify the method of Vary et al. with the bumper primer of Schram et al. for extension and amplification.

Regarding Claim 60, Vary et al. teach the method of Claim 55 wherein the label becomes detectable upon extension of the primer due to the incorporation of labeled nucleotides (Column 3, lines 54-59, Fig 1E and Fig 4F)

Regarding Claim 61, Vary et al. teach the method of Claim 55, but they do not teach the label is a fluorescent donor/quencher dye. However, Walker et al. teach a similar method for detecting a single nucleotide difference in a target sequence by detection of the detector primer extension wherein the label is a fluorescent donor/quencher i.e. fluorescence energy transfer (Column 12, lines 51-57). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Walker et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the label of Vary with the donor/quencher of Walker et al. for the known benefit of simple and convenient detection without product isolation as taught by Walker et al. (Column 12, lines 49-50).

Regarding Claim 62, Vary et al. teach the method wherein the diagnostic nucleotide is a 3' terminal nucleotide (Column 8, lines 5-61).

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
September 14, 2000